

Surgery by Consultant Gynecologic Oncologists Improves Survival in Patients with Ovarian Carcinoma

Mirjam J. A. Engelen, M.D.¹

Henrike E. Kos, M.Sc.²

Pax H. B. Willemse, Ph.D.³

Jan G. Aalders, Ph.D.¹

Elisabeth G. E. de Vries, Ph.D.³

Michael Schaapveld, Ph.D.²

Renee Otter, Ph.D.²

Ate G. J. van der Zee, Ph.D.¹

¹ Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, University Medical Center Groningen, Groningen, The Netherlands.

² Department of Epidemiology and Statistics, Comprehensive Cancer Center North Netherlands, Groningen, The Netherlands.

³ Division of Medical Oncology, Department of Internal Medicine, University Medical Center Groningen, Groningen, The Netherlands.

Supported by the Comprehensive Cancer Center North Netherlands.

The authors thank all registry clerks of the Comprehensive Cancer Center North for their meticulous data acquisition.

Address for reprints: Ate G. J. van der Zee, Ph.D., Department of Obstetrics and Gynecology, CMC 5, University Medical Center Groningen, P.O. Box 30001, 9700 RB Groningen, The Netherlands; Fax: (011) 31 503611806; E-mail: a.g.j. van.der.zee@og.umcg.nl

Received April 8, 2005; revision received July 31, 2005; accepted August 16, 2005.

© 2005 American Cancer Society

DOI 10.1002/cncr.21616

Published online 20 December 2005 in Wiley InterScience (www.interscience.wiley.com).

BACKGROUND. Consultant gynecologic oncologists from the regional Comprehensive Cancer Center assisted community gynecologists in the surgical treatment of patients with ovarian carcinoma when they were invited. For this report, the authors evaluated the effects of primary surgery by a gynecologic oncologist on treatment outcome.

METHODS. The hospital files from 680 patients with epithelial ovarian carcinoma who were diagnosed between 1994 and 1997 in the northern part of the Netherlands were abstracted. Treatment results were analyzed according to the operating physician's education by using survival curves and univariate and multivariate Cox regression analyses.

RESULTS. Primary surgery was performed on 184 patients by gynecologic oncologists, and on 328 patients by general gynecologists. Gynecologic oncologists followed surgical guidelines more strictly compared with general gynecologists (patients with International Federation of Gynecology and Obstetrics [FIGO] Stage I–II disease, 55% vs. 33% [$P = 0.01$]; patients with FIGO Stage III disease, 60% vs. 40% [$P = 0.003$]) and more often removed all macroscopic tumor in patients with FIGO Stage III disease (24% vs. 12%; $P = 0.02$). When patients were stratified according to FIGO stage, the 5-year overall survival rate was 86% versus 70% ($P = 0.03$) for patients with Stage I–II disease and 21% versus 13% ($P = 0.02$) for patients with Stage III–IV disease who underwent surgery by gynecologic oncologists and general gynecologists, respectively. The hazards ratio for patients who underwent surgery by gynecologic oncologists was 0.79 (95% confidence interval [95%CI], 0.61–1.03; adjusted for patient age, disease stage, type of hospital, and chemotherapy); when patients age 75 years and older were excluded, the hazards ratio fell to 0.71 (95% CI, 0.54–0.94) in multivariate analysis.

CONCLUSIONS. The surgical treatment of patients with ovarian carcinoma by gynecologic oncologists occurred more often according to surgical guidelines, tumor removal more often was complete, and survival was improved. *Cancer* 2006;106:589–98. © 2005 American Cancer Society.

KEYWORDS: general gynecologist, gynecologic oncologist, gynecologic carcinoma, medical oncologist, patterns of care, primary surgery.

Patients with ovarian carcinoma have the worst prognosis of all patients with gynecologic malignancies. Their overall 5-year survival rate approximates 40%, mainly due to the large proportion of patients who present with advanced disease. The life-time risk of developing ovarian carcinoma is 1 in 75.¹ In the Netherlands, with a population of 17 million, there are 1100 newly diagnosed patients each year, for an average of 1–2 new patients per year for every gynecologist. The treatment of ovarian carcinoma is multidisciplinary in nature. Chemotherapy has had a major impact on survival and, currently, most patients receive platinum-containing combinations.² Over a decade ago, when not all patients received platinum-contain-

ing chemotherapy, the effect of cytoreductive surgery on survival was considered minor compared with the impact of platinum.³ Currently, however, with virtually all patients with advanced stage disease receiving platinum, optimal cytoreduction is considered an important tool to improve survival.⁴

Surgery is important to determine the correct disease stage and to remove as much tumor as possible in patients.⁵⁻⁸ Several studies have shown that patients with ovarian carcinoma who underwent surgery by a gynecologist had better survival compared with patients who underwent surgery by a general surgeon.⁹⁻¹² Subsequently, it was suggested that surgery by a gynecologic oncologist would improve survival further.^{13,14} However, that hypothesis could not be confirmed in a large population-based study on differences in patterns of care of patients with ovarian carcinoma.¹⁰ In a more recent population-based study on the impact of surgery by a gynecologic oncologist compared with a general gynecologist, a survival benefit was found for patients with International Federation of Gynecology and Obstetrics (FIGO) Stage III disease.¹⁵ The results of that study cannot be generalized because patients with nonepithelial tumors also were included in the study population, and the effect of treatment in teaching hospitals was not addressed. However, because it also was found that gynecologic oncologists attained optimal cytoreduction more often compared with general gynecologists,¹⁶ it is expected that survival will be improved when surgery is performed by gynecologic oncologists.

The Comprehensive Cancer Center North covers the northern part of the Netherlands, a mainly rural area with a population of approximately 2.1 million. Within our region, guidelines regarding the diagnosis and treatment for most malignancies have been developed and revised since the middle 1970s. The Working Party on Gynecological Tumors, which includes gynecologists, medical oncologists, pathologists, and radiotherapists, believed that, especially in the smaller hospitals, which treated < 10 patients with ovarian carcinoma per year, treatment results needed improvement. Since 1980, gynecologic oncologists at our regional university hospital regularly have assisted their fellow gynecologists in the community hospitals when performing surgery on patients with suspected ovarian carcinoma. The difference in patterns of care offered to patients with ovarian carcinoma in our region provides a perfect, natural, population-based experiment for studying the effect of surgery by a gynecologic oncologist on the quality of surgery and the outcome of patients. The results of this natural experiment are presented herein.

MATERIALS AND METHODS

The medical charts of 680 consecutive patients who were diagnosed with epithelial ovarian carcinoma between January 1994 and January 1998 in the northern part of the Netherlands were reviewed. Patients were identified from the Regional Cancer Registry of the Comprehensive Cancer Center North. Data were collected on a specifically designed case-report form by registry clerks of the Cancer Center. The case-report forms were monitored by one of the authors (M.J.A.E.). The data gathered from the inpatient and outpatient hospital files included comorbidity, for which an adapted Charlson score¹⁷ was used, the results from diagnostic tests, the surgery reports, the pathology reports, information on additional treatments (including chemotherapy and radiotherapy), and follow-up. Most attention was paid to the surgical procedures undertaken. Findings at inspection and palpation were noted along with which tissues and organs were removed, whether there was spill, residual tumor (size and location), the amount of blood loss, and complications.

Regional Guidelines

Guidelines on the diagnostic work-up, surgical and medical treatment, and follow-up of patients with ovarian carcinoma are made and revised regularly by the regional Working Party on Gynecological Tumors. The surgical guidelines largely resemble FIGO guidelines.¹⁸ For statistical analysis in the current study, treatment according to surgical guidelines was defined as total abdominal hysterectomy and bilateral salpingo-oophorectomy, (partial) omentectomy, at least one lymph node removed, and at least one peritoneal biopsy taken for patients with early-stage disease; and as total abdominal hysterectomy and bilateral salpingo-oophorectomy and (partial) omentectomy for patients with Stage III disease. When the uterus or one ovary already had been removed before the current procedure, removal of the remaining organs was considered guideline treatment. Patients with FIGO Stage IV disease were left out of the analyses concerning correct surgical staging because uniform surgical guidelines were lacking for Stage IV disease.

The regional guidelines also advise on adjuvant treatment. In the first half of the study period, adjuvant chemotherapy (the first choice was six cycles of cyclophosphamide and carboplatin) was advised for all stages and grades of disease except for Stage IA, IB, and IIA well differentiated tumors in patients without residual tumor. Age older than 70 years and a creatinine clearance < 60 mL/minute were regarded as contraindications, and the second choice (melphalan) was advised for those patients. In the second half of the study period, these contraindications were re-

garded as relative, and chemotherapy was advised for all stages except Stage IA and IB well differentiated tumors in patients without residual tumor. The first choice remained cyclophosphamide with carboplatin, and paclitaxel was introduced as second-line treatment.

Statistical Analysis

Differences between patients who underwent surgery by general gynecologists and patients who underwent surgery by gynecologic oncologists were assessed using the Kruskal–Wallis test for continuous variables and the chi-square test for categorical variables. The survival of patients who underwent surgery was calculated as the difference between date of first surgical procedure and either the date of death or the date of last patient contact for patients who did not die during follow-up. Because the exact dates of disease progression or recurrence were not scored in a standard manner, we choose overall survival as the only endpoint. Observed survival rates were estimated by using the Kaplan–Meier method. The log-rank test was used to assess differences in survival between patients who underwent surgery by a gynecologic oncologist and patients who underwent surgery by a general gynecologist, with the patients stratified into a group with early-stage disease (FIGO Stage I–II) and a group with late-stage disease (FIGO Stage III–IV). In multivariate analyses, a Cox proportional hazards model was used to assess the effect of the type of surgeon (gynecologic oncologist or general gynecologist) on survival adjusted for prognostic variables, hospital of surgery, and chemotherapy. Variables entered the model as a confounder when β estimates of the type of surgeon changed by $> 10\%$. The proportional hazards assumption was confirmed by inspection of $\log(-\log[\text{survival}])$ curves and by examination of time-dependent covariates. P values ≤ 0.05 were considered significant. All analyses were conducted using SPSS software (version 11.0; SPSS Inc., Chicago, IL).

RESULTS

Patients

Apart from the University Hospital, our region is comprised of 13 general hospitals and 3 teaching hospitals that participate in the training of medical specialists. The annual number of new patients with ovarian carcinoma in the different hospitals varies from 2 patients to 24 patients. The largest numbers (20–24 new patients per hospital annually) were treated in the 3 teaching hospitals. Gynecologists in these hospitals only incidentally will call for the assistance of their academic colleagues (8% of first procedures). The smaller nonteaching hospitals, which treat 2–11 new

patients annually, used this service for 42% of first surgical procedures (range, 0–76% of first procedures).

The current study population consisted of all 680 patients who were diagnosed with epithelial ovarian carcinoma between January 1994 and January 1998 in the northern part of the Netherlands. Forty-eight patients were excluded; no data could be retraced in 9 patients, 9 patients were diagnosed at autopsy, 5 patients were treated outside of our region, the original diagnosis of primary ovarian carcinoma had changed in 11 patients (2 patients had borderline ovarian tumors, 2 patients had nonepithelial ovarian tumors, and 7 patients had tumors located in other primary sites), 12 patients were diagnosed concurrently with a second malignancy other than carcinoma of the endometrium or skin, and 2 patients were included twice in the data base. Having a prior malignancy was no reason for exclusion from the study. Therefore, the study population was comprised of 632 patients.

Thirty-four patients who had incomplete surgical staging procedures underwent a second surgical staging. In these patients, findings from the first surgery and the restaging procedure were combined and analyzed statistically as a single procedure. Those who underwent surgery by general surgeons ($n = 25$ patients) for the most part were patients with suspected colon carcinoma. In general, these patients were older and had a higher disease stage (FIGO Stage IV, 32%) compared with patients who underwent surgery by gynecologists. On univariate survival analysis, the patients who underwent surgery by a general surgeon had a hazards ratio of 3.70 (95% confidence interval [95% CI], 2.33–5.89) compared with patients who underwent surgery by a gynecologic oncologist. Because the patients who underwent surgery by a general surgeon were not comparable to the patients who underwent surgery by a gynecologist, and because we were interested in possible (dis)advantages of surgery by gynecologic oncologists compared with surgery by general gynecologists, the patients who underwent surgery by a general surgeon were excluded from further analyses along with two patients for whom the type of operating surgeon was unknown.

Ninety-three of 632 patients (14.7%) did not undergo primary surgery. Six patients underwent intervention surgery after they received primary chemotherapy. The remaining 87 patients, who did not undergo surgery, had a median age of 81 years (range, 42–93 yrs). Thirteen percent of patients were staged clinically with at least FIGO Stage I–II disease, 16% of patients had Stage III disease, 48% of patients had Stage IV disease, and the stage of disease was unknown in 23% of patients. No treatment was instituted in 56 patients. Reasons for withholding treatment were patient wishes, age, comorbidity, or a combina-

TABLE 1
Characteristics of Patients with Ovarian Carcinoma who Underwent Primary Surgical Procedures

Characteristic	General gynecologist		Gynecologic oncologist		P value
	No. of patients	%	No. of patients	%	
Age					
Median (yrs)	65		60		0.002
Range (yrs)	16-92		25-87		
< 40 yrs	14	4.2	14	7.6	0.01
40-49 yrs	53	16.2	33	17.9	
50-59 yrs	70	21.3	41	22.3	
60-69 yrs	73	22.3	55	29.9	
70-79 yrs	85	25.9	36	19.6	
≥ 80 yrs	33	10.1	5	2.7	
FIGO stage					
Stage I	97	29.6	48	26.1	0.17
Stage II	38	11.6	17	9.2	
Stage III	142	43.3	98	53.3	
Stage IV	51	15.5	21	11.4	
Tumor grade					
1	53	16.2	31	16.8	0.93
2	81	24.7	44	23.9	
3-4	132	40.2	78	42.2	
Unknown	62	18.9	31	16.8	
Histology					
Serous	179	54.6	84	45.7	0.003
Mucinous	31	9.5	33	17.9	
Endometrioid	21	6.4	23	12.5	
Clear cell	20	6.1	13	7.1	
Adenocarcinoma NOS/unclassified	77	23.5	31	16.8	
Preoperative CA 125					
≤ 35 U/mL	50	15.2	27	14.7	0.02
> 35 U/mL	234	71.3	147	79.9	
Unknown	44	13.4	16	5.4	
Comorbidity					
No	228	69.5	135	73.4	0.36
Yes	100	30.5	49	26.6	
Ascites					
Absent	97	29.6	48	26.1	0.21
Present	211	64.3	130	70.7	
Unknown	20	6.1	6	3.3	
Hospital of surgery					
Teaching	184	56.1	64	34.8	< 0.001
Nonteaching	144	43.9	120	65.2	
Chemotherapy					
No	95	29.0	33	17.9	< 0.001
Yes, platinum	188	57.3	138	75.0	
No platinum	45	13.7	13	7.1	
Total no. of patients	328		184		

FIGO: International Federation of Gynecology and Obstetrics; NOS: not otherwise specified.

tion thereof in 39 patients; noneligible performance status in 12 patients; and unknown reasons in 5 patients.

The characteristics of 512 patients who underwent primary surgery by a gynecologist are summarized in Table 1, which shows that patients who underwent surgery by a gynecologic oncologist were younger and more often underwent surgery in a nonteaching hospital (by a visiting gynecologic oncologist) compared

with patients who underwent surgery by a general gynecologist. Among the patients who were treated by a gynecologic oncologist, 85% received chemotherapy, when indicated, which contained a platinum compound in 91% of patients. In the patients who were treated by a general gynecologist, 75% of patients received chemotherapy, if indicated, which contained a platinum compound in 81% of patients. The percent-

TABLE 2
Surgical Procedures Undergone by 440 Patients with International FIGO Stage I, II, and III Ovarian Carcinoma

Surgical procedure	FIGO Stage I-II				P value	FIGO Stage III				P value
	General gynecologist		Gynecologic oncologist			General gynecologist		Gynecologic oncologist		
	No.	%	No.	%		No.	%	No.	%	
Salpingo-oophorectomy										
No	1	0.7	—		0.45	32	22.5	13	13.3	0.13
Unilateral	20	14.8	4	6.2		16	11.3	6	6.1	
Bilateral	16	11.9	9	13.8		28	19.7	18	18.4	
Bilateral with hysterectomy	96	71.1	51	78.5		61	43.0	56	57.1	
Unknown	2	1.5	1	1.5		5	3.5	5	5.1	
Omentectomy										
No	46	34.1	5	7.7	< 0.001	23	16.2	2	2.0	0.002
Total/partial	89	65.9	58	89.2		116	81.7	93	94.9	
Unknown	—		2	3.1		3	2.1	3	3.1	
Biopsy										
None	33	24.4	3	4.6	< 0.001					
≥ 1	59	43.7	48	73.8						
Unknown	43	31.9	14	21.5						
Pelvic and/or paraaortic lymph node sampling/lymphadenectomy										
No	90	66.7	25	38.5	< 0.001					
Yes	41	30.4	40	61.5						
Unknown	4	3.0	—							
Postoperative residual tumor										
No macroscopic	113	83.7	60	92.3	0.50	15	10.6	22	22.4	0.09 ^a
< 2 cm	6	4.4	2	3.1		22	15.5	18	18.4	
> 2 cm	2	1.5	—			45	31.7	25	25.5	
Size unknown	3	2.2	1	1.5		43	30.3	26	26.5	
Unknown	11	8.1	2	3.1		17	12.0	7	7.1	
Postoperative complications										
None	125	92.6	54	83.1	0.04	114	80.3	82	83.7	0.61
≥ 1	10	7.4	11	16.9		28	19.7	16	16.3	
Perioperative death										
No	135	100	65	100	—	137	96.5	97	99.0	0.41
Yes	—		—			5	3.5	1	1.0	
Surgical guidelines										
Not followed	61	45.2	23	35.4	0.01 ^b	81	57.0	36	36.7	0.01 ^b
Followed	30	22.2	28	43.1		53	37.3	55	56.1	
Unknown	44	32.6	14	21.5		8	5.6	7	7.1	
Total no. of patients	135		65			142		98		

FIGO: International Federation of Gynecology and Obstetrics.

^a $P = 0.02$, residual tumor mass versus no residual tumor mass (unknown not included); $P = 0.05$, residual tumor mass < 2 cm versus residual tumor mass > 2 cm (unknown size not included).

^b $P = 0.01$ for International Federation of Gynecology and Obstetrics (FIGO) Stage I-II ovarian carcinoma and $P = 0.003$ for FIGO Stage III ovarian carcinoma (unknown not included).

ages of patients who received chemotherapy if indicated and the percentages of patients who received a platinum compound differed ($P = 0.01$) between gynecologic oncologists and general gynecologists. In only 5% of 512 patients, chemotherapy was not indicated, because those patients were diagnosed with well differentiated Stage IA or IB disease.

Surgery

In Table 2, the details of the surgical staging and debulking procedures are shown for patients with

FIGO Stage I–III ovarian carcinoma. In patients with Stage I–II disease, (partial) omentectomy and lymph node sampling or lymphadenectomy were performed more often by gynecologic oncologists compared with general gynecologists ($P < 0.001$ for both). In patients with FIGO Stage III disease, more patients underwent complete debulking surgery by gynecologic oncologists (24% vs. 12%; $P = 0.02$). Furthermore, 62% of patients with FIGO Stage III disease who underwent surgery by a gynecologic oncologist were left with residual tumor masses that measured < 2 cm in great-

est dimension compared with 45% of patients who underwent surgery by general gynecologists ($P = 0.05$). The amount of residual tumor in patients with FIGO Stage III disease had a major impact on survival, with 5-year survival rates of 54% for patients with no residual disease, 15% for patients who had residual disease masses that measured < 2 cm in greatest dimension, and 6% for patients who had more residual disease ($P < 0.001$). In all disease stages, patients more often received surgical treatment according to prevailing surgical guidelines when they underwent surgery by a gynecologic oncologist (patients with FIGO Stage I–II disease, $P = 0.01$; patients with FIGO Stage III disease, $P = 0.003$; chi-square test). The risk of dying for patients who did not undergo surgery according to surgical guidelines was almost twice the risk for patients who underwent surgery according to the guidelines. For patients with FIGO Stage I–II disease, the 5-year survival rate was 84% when guidelines were followed and 73% when guidelines were not followed (hazards ratio, 1.95; 95% CI, 0.82–4.63 [$P = 0.13$]); for patients with FIGO Stage III disease, the 5-year survival rates were 32% and 11%, respectively (hazards ratio, 1.97; 95% CI, 1.45–2.68 [$P < 0.001$]). The survival advantage for patients who underwent surgery according to the guidelines remained nearly unchanged in an exploratory multivariate analysis that compared the survival of these patients with the survival of patients in whom surgical guidelines were not followed (adjusted for patient age, disease stage, and chemotherapy; hazards ratio, 1.79; 95% CI, 1.33–2.41 [$P < 0.001$]).

Survival

Figure 1 shows that the 5-year survival rate for patients who had FIGO Stage I–II ovarian carcinoma was 86% when surgery was performed by a gynecologic oncologist and 70% when surgery was performed by a general gynecologist ($P = 0.03$). For patients who had FIGO Stage III–IV disease, the 5-year survival rates were 21% (median survival, 23 mos) and 13% (median survival, 15 mos) ($P = 0.02$), respectively (Fig. 2). In univariate analysis, age, FIGO stage, tumor grade, mucinous or endometrioid histotype, the presence of ascites, an elevated serum CA 125 level, comorbidity, and residual tumor all were found to be significant prognostic factors in the study population, as shown in Table 3.

Multivariate Analysis

In a Cox proportional hazards analysis, the crude hazards ratio (risk of dying) was 0.82 (95% CI, 0.64–1.05) for patients who underwent surgery by a gynecologic oncologist versus a general gynecologist. The presence of ascites, preoperative CA 125 level,

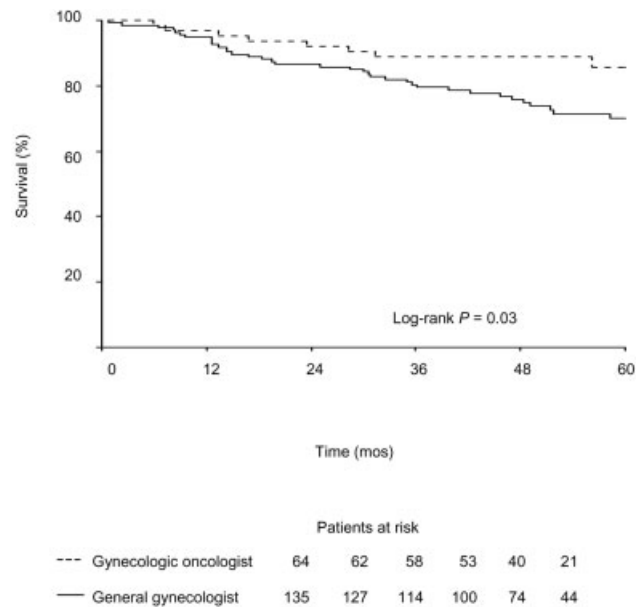


FIGURE 1. Crude overall 5-year survival in patients with International Federation of Gynecology and Obstetrics Stage I–II ovarian carcinoma who underwent surgery performed by gynecologic oncologists and surgery performed by general gynecologists.

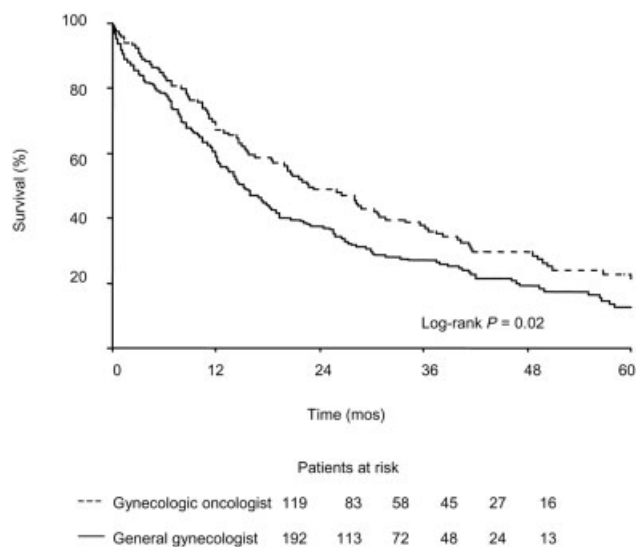


FIGURE 2. Crude overall 5-year survival in patients with International Federation of Gynecology and Obstetrics Stage III–IV ovarian carcinoma who underwent surgery performed by gynecologic oncologists and surgery performed by general gynecologists.

and comorbidity did not appear to affect the correlation between type of gynecologist and survival. However, patient age, disease stage, and the type of hospital (teaching or nonteaching) were found to affect this relation and therefore required adjustment. When we adjusted for age, stage, and type of hospital, the hazards ratio of surgery by a gynecologic

TABLE 3
Univariate Cox Proportional Hazards Analysis of Patients who Underwent a Primary Surgical Procedure

Variable	No. of patients	No. of deaths	HR	95% CI	P value
Surgeon					0.11
General gynecologist	183	194	1.00		
Gynecologic oncologist	326	98	0.82	0.64–1.05	
Patient age					< 0.001
< 50 yrs	114	39	1.00		
50–59 yrs	109	61	1.81	1.21–2.70	
60–69 yrs	128	69	1.86	1.26–2.76	
≥ 70 yrs	158	123	3.87	2.70–5.56	
FIGO stage					< 0.001
Stage I	144	24	1.00		
Stage II	55	20	2.46	1.36–4.46	
Stage III	238	183	7.80	5.09–11.96	
Stage IV	72	65	15.98	9.93–25.71	
Tumor grade					< 0.001
Grade 1	84	26	1.00		
Grade 2	124	67	2.15	1.37–3.38	
Grade 3–4	209	147	3.34	2.20–5.08	
Unknown	92	52	2.16	1.35–3.46	
Histology					< 0.001
Serous	262	169	1.00		
Mucinous	64	23	0.46	0.29–0.70	
Endometroid	43	12	0.32	0.18–0.58	
Clear cell	33	16	0.69	0.41–1.15	
Adenocarcinoma, NOS	107	72	1.18	0.89–1.55	
Preoperative CA 125					< 0.001
≤ 35 U/mL	76	20	1.00		
> 35 U/mL	380	241	3.31	2.10–5.22	
Unknown	53	31	2.79	1.59–4.90	
Comorbidity					< 0.001
No	360	188	1.00		
Yes	149	104	1.69	1.33–2.15	
Ascites					< 0.001
Absent	143	50	1.00		
Present	340	230	2.63	1.98–3.51	
Unknown	26	12	1.53	0.87–2.71	
Residual tumor					< 0.001
No macroscopic	217	53	1.00		
< 2 cm	59	44	4.37	2.93–6.53	
> 2 cm	96	87	8.14	5.76–11.52	
Unknown	137	108	5.52	3.97–7.69	
Hospital of surgery					0.29
Teaching	246	136	1.00		
Nonteaching	263	156	1.13	0.90–1.43	

HR: hazards ratio; 95% CI: 95% confidence interval; FIGO: International Federation of Gynecology and Obstetrics; NOS: not otherwise specified.

logic oncologist was 0.77 (95% CI, 0.60–1.00) (Table 4). When chemotherapy was included in the model, because platinum-based chemotherapy in particular was prescribed more often to patients who underwent surgery by a gynecologic oncologist, the hazards ratio became 0.79 (95% CI, 0.61–1.03). Younger patients especially appeared to benefit from specialized surgical treatment, because, after correcting for age, stage, type of hospital, and chemotherapy, the hazards ratio fell to 0.71 (95% CI,

0.54–0.94) when patients older than age 75 years were excluded (leaving 431 patients for analysis).

DISCUSSION

The phenomenon of traveling gynecologic oncologists assisting general gynecologists in community hospitals in the northern region of the Netherlands gave us the unique opportunity to explore the impact of surgery by gynecologic oncologists on patients with ovarian carcinoma. In the current, population-based

TABLE 4
Cox Multivariate Model Adjusted for the Impact of Covariates on the Difference in Risk of Dying (HR) for Patients with Ovarian Carcinoma who Underwent Surgery Performed by Gynecologic Oncologists Compared with Patients who Underwent Surgery Performed by General Gynecologists

Crude survival difference, all stages	HR	95% CI	P value
Univariate			
General gynecologist	1.00		
Gynecologic oncologist	0.82	0.64–1.05	0.11
Adjusted for age, stage, and type of hospital			
General gynecologist	1.00		
Gynecologic oncologist	0.77	0.60–1.00	0.05
Adjusted for age, stage, type of hospital, and chemotherapy			
General gynecologist	1.00	0.61–1.03	
Gynecologic oncologist	0.79		0.08
Adjusted for age, stage, type of hospital, chemotherapy, and age < 76 yrs			
General gynecologist	1.00		
Gynecologic oncologist	0.71	0.54–0.94	0.02

HR: hazards ratio; 95% CI: 95% confidence interval.

study, we were able to correct for all kinds of possible confounding factors, such as patient selection and hospital type, which often was not possible in previously published studies concerning the impact of surgery by gynecologic oncologists on survival in patients with ovarian carcinoma. The results of the current study indicate clearly that surgery by a gynecologic oncologist indeed improves survival, because the multivariate analysis demonstrated a 23% reduction in the risk of dying for patients who underwent surgery by gynecologic oncologists after adjusting for patient age, disease stage, and the type of hospital. After an additional adjustment for chemotherapy, the reduction in the risk of dying became 21% (no longer significant; $P = 0.08$), most likely due to the relatively small numbers. However, when patients older than age 75 years were excluded from the analysis, the reduction in risk of dying became 29% ($P = 0.02$), suggesting that younger patients in particular benefit from surgery by gynecologic oncologists.

The overall survival of patients with late-stage ovarian carcinoma, as presented in the current study, may appear to be low on first sight, with 5-year survival rates of 21% and 13% for patients who underwent surgery by gynecologic oncologists and general gynecologists, respectively. However, our rates are comparable to those reported from other population-based studies. A Scottish group (Junor et al.¹⁵) reported 3-year survival rates of 20% for patients with FIGO Stage III disease and 6% for patients with FIGO Stage IV disease and reported a median survival of 18 months and 13 months for patients with Stage III

disease who underwent surgery by gynecologic oncologists and general gynecologists, respectively (in our population, the median survival was 23 mos and 15 mos, respectively). In Utah, a median survival of 26 months versus 16 months was observed for patients with ovarian carcinoma who had late-stage disease treated by gynecologic oncologists versus general gynecologists, respectively.¹⁵ In addition, a Norwegian group (Tingulstad et al.¹⁹), reporting results from a case-control study regarding the centralization of treatment for ovarian carcinoma, observed 5-year survival rates of 26% and 4% for patients with advanced-stage ovarian carcinoma who underwent surgery by gynecologic oncologists and general gynecologists, respectively.^{14,15,19}

It has been postulated before that patients with ovarian carcinoma should be treated by gynecologic oncologists, because this may improve their survival.^{20,21} In ovarian carcinoma, residual tumor mass after first surgery has a major impact on survival, and the current results showed that complete cytoreduction was attained more often by gynecologic oncologists than by general gynecologists in patients with FIGO Stage III disease. Moreover, 62% of patients with FIGO Stage III disease who underwent surgery by a gynecologic oncologist were left with residual tumor masses that measured < 2 cm in greatest dimension compared with 45% of patients who underwent surgery by general gynecologists. In their meta-analysis on cytoreductive surgery for ovarian carcinoma, Bristow et al. reported a weighted mean percentage of optimal debulking (defined as the greatest dimension of residual disease < 1–2 cm in 95% of selected studies) of 42% for a mix of operating physicians.⁴ Eisenkop and Spirtos published a survey among gynecologic oncologists on optimal debulking rates and reported optimal debulking in 70% of patients with FIGO Stage IIIC disease.²²

Apart from residual tumor mass, another major issue that may influence patient survival is treatment according to prevailing guidelines. Guidelines for the treatment of ovarian carcinoma have been published by regional, national, and international organizations.²³ We observed greater compliance with surgical guidelines among gynecologic oncologists than among general gynecologists. Furthermore, patients with Stage I–II and Stage III ovarian carcinoma who underwent surgery according to the guidelines had a better survival.

Stage migration, which means that, through adequate staging, patients are assessed correctly with a more advanced stage of disease, cannot be excluded to account in part for the survival benefit of patients who undergo surgery performed by gynecologic oncologists when comparing survival figures in the dif-

ferent stages. However, in the current study, this survival benefit was found consistently in all patient subgroups.

Data that lead to findings comparable to those in the current study have been presented previously in other studies. However, the interpretation of many of those (older) studies is hampered by their association with important flaws. Such flaws also have prevented the gynecologic community as a whole from accepting and implementing the conclusions from those studies in the daily practice for patients with suspected ovarian carcinoma. A first example of a major flaw in many previous population-based studies is that survival analyses of patients who underwent surgery by general gynecologists often were mixed with survival analyses of patients who underwent surgery by general surgeons.^{13,14} Our current results show that survival was especially poor for patients with ovarian carcinoma who underwent surgery by general surgeons, which also has been reported in other studies⁹⁻¹²; however, our results also showed that patients who underwent surgery by general surgeons differed from patients who underwent surgery by gynecologists. The majority of those patients already had gastrointestinal complaints and underwent surgery because of suspected colon carcinoma. Moreover, those patients were older and had higher FIGO stage disease. Differences in age, stage, or histotype of patients treated by general surgeons compared with gynecologists also have been noted previously; however, previous investigators did not report on the most important characteristic, namely, the presumptive preoperative diagnosis that indicated advanced-stage disease, that we present in the current study.^{9,11,12} Because of this clear patient selection bias, patients who undergo surgery by general surgeons should be excluded from comparative analyses between patients who do or do not undergo surgery by gynecologic oncologists in population-based studies in ovarian carcinoma.

Another important flaw in comparative survival analyses of patients with ovarian carcinoma is the possible beneficial influence of treatment in a teaching hospital.²⁴ The advantage of undergoing surgery in a teaching hospital, which also was found in our multivariate analysis, is not understood easily. In subgroup analyses, the variables of patient age, disease stage, and type of first-course chemotherapy were excluded as explanations. Surgeon's patient volume also was found to have no significant influence on survival. Possibly, the explanation may be sought in more subtle issues, such as the dose of chemotherapy given, the treatment of recurrent disease, the type and dosage of second-line chemotherapy, etc. Because the teaching hospitals also had much larger caseloads per hospital, hospital volume may be the more correct term for the

effect found.²⁵ The issue of beneficial influence of treatment in a teaching hospital was not addressed in the one population-based study that is most comparable to our current work¹⁵ or in the Norwegian case-control study regarding the centralization of primary surgery in patients with ovarian carcinoma.¹⁹

Finally, the third major issue that, in many population-based studies, may bias patient survival analyses in favor of gynecologic oncologists, is patient selection. In our multivariate analysis, however, we were able to correct for patient selection by adjusting for disease stage, patient age, teaching hospital, and chemotherapy, thereby excluding patient selection as a possible explanation for the observed better survival of patients who underwent surgery by gynecologic oncologists.

When implementing the conclusion from the current study that patients with ovarian carcinoma optimally should undergo surgery by gynecologic oncologists, two important topics should be addressed. First, the referral of every patient who has a pelvic mass to cancer centers will prove to be hard because of problems with logistics and manpower. In this respect, a triage system may be applied to allow the identification of patients who have a low likelihood of ovarian carcinoma,²⁶ or the referral guidelines of the Society of Gynecologic Oncologists and the American College of Obstetricians and Gynecologists can be followed.²⁷ Second, in patients who have a nonsuspected ovarian carcinoma removed suboptimally by a general gynecologist, a relaparotomy should be considered.²⁸ Disease restaging is worthwhile, especially in patients with apparently early-stage ovarian carcinoma, because adjuvant chemotherapy does not appear to improve survival in optimally staged patients with early-stage disease.²⁹ In patients with apparently advanced-stage disease that was not debulked optimally by a general gynecologist, either direct relaparotomy by a gynecologic oncologist or intervention surgery after response to three cycles of chemotherapy may be considered.^{30,31}

The results of the current study demonstrate clearly that surgery by a gynecologic oncologist has a positive effect on survival, reducing the risk of dying by > 20% for patients with ovarian carcinoma. Specific surgical training appeared to be important, because a surgeon's patient volume alone had no effect on survival. Receiving treatment in a teaching hospital also improved survival. These results imply that every patient who has suspected ovarian carcinoma deserves to undergo surgery performed by a gynecologic oncologist. For the short term, a traveling gynecologic oncologist may be an acceptable alternative to the referral of all patients with ovarian carcinoma to a center with gynecologic oncologists. However, care

should be taken that correct surgical treatment is followed by the right additional chemotherapy, particularly in smaller hospitals, in which the caseload for the medical oncologist is as low as that for the gynecologist. In the future, our objective should be to concentrate the treatment of patients who have ovarian carcinoma in teaching hospitals with gynecologic oncologists.

REFERENCES

- Holschneider CH, Berek JS. Ovarian cancer: epidemiology, biology, and prognostic factors. *Semin Surg Oncol*. 2000;19:3–10.
- Cannistra SA. Cancer of the ovary. *N Engl J Med*. 2004;351:2519–2529.
- Hunter RW, Alexander ND, Soutter WP. Meta-analysis of surgery in advanced ovarian carcinoma: is maximum cytoreductive surgery an independent determinant of prognosis? *Am J Obstet Gynecol*. 1992;166:504–511.
- Bristow RE, Tomacruz RS, Armstrong DK, Trimble EL, Montz FJ. Survival effect of maximal cytoreductive surgery for advanced ovarian carcinoma during the platinum era: a meta-analysis. *J Clin Oncol*. 2002;20:1248–1259.
- Young RC, Decker DG, Wharton JT, et al. Staging laparotomy in early ovarian cancer. *JAMA*. 1983;250:3072–3076.
- Mayer AR, Chambers SK, Graves E, et al. Ovarian cancer staging: does it require a gynecologic oncologist? *Gynecol Oncol*. 1992;47:223–227.
- Griffiths CT. Surgical resection of tumor bulk in the primary treatment of ovarian carcinoma. *J Natl Cancer Inst Monogr*. 1975;42:101–104.
- Griffiths CT, Parker LM, Fuller-AF Jr. Role of cytoreductive surgical treatment in the management of advanced ovarian cancer. *Cancer Treat Rep*. 1979;63:235–240.
- Kehoe S, Powell J, Wilson S, Woodman C. The influence of the operating surgeon's specialisation on patient survival in ovarian carcinoma. *Br J Cancer*. 1994;70:1014–1017.
- Nguyen HN, Averette HE, Hoskins W, Penalver M, Sevin BU, Steren A. National survey of ovarian carcinoma. Part V. The impact of physician's specialty on patients' survival. *Cancer*. 1993;72:3663–3670.
- Woodman C, Baghdady A, Collins S, Clyma JA. What changes in the organisation of cancer services will improve the outcome for women with ovarian cancer? *Br J Obstet Gynaecol*. 1997;104:135–139.
- Junor EJ, Hole DJ, Gillis CR. Management of ovarian cancer: referral to a multidisciplinary team matters. *Br J Cancer*. 1994;70:363–370.
- Eisenkop SM, Spirtos NM, Montag TW, Nalick RH, Wang HJ. The impact of subspecialty training on the management of advanced ovarian cancer. *Gynecol Oncol*. 1992;47:203–209.
- Carney ME, Lancaster JM, Ford C, Tsodikov A, Wiggins CL. A population-based study of patterns of care for ovarian cancer: who is seen by a gynecologic oncologist and who is not? *Gynecol Oncol*. 2002;84:36–42.
- Junor EJ, Hole DJ, McNulty L, Mason M, Young J. Specialist gynaecologists and survival outcome in ovarian cancer: a Scottish national study of 1866 patients. *Br J Obstet Gynaecol*. 1999;106:1130–1136.
- Olaitan A, Weeks J, Mocroft A, Smith J, Howe K, Murdoch J. The surgical management of women with ovarian cancer in the south west of England. *Br J Cancer*. 2001;85:1824–1830.
- Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. 1987;40:373–383.
- FIGO Cancer Committee. Staging announcement. *Gynecol Oncol*. 1986;25:383–385.
- Tingulstad S, Skjeldestad FE, Hagen B. The effect of centralization of primary surgery on survival in ovarian cancer patients. *Obstet Gynecol*. 2003;102:499–505.
- Junor E. The impact of specialist training for surgery in ovarian cancer. *Int J Gynecol Cancer*. 2000;10:16–18.
- Orr JW Jr. What constitutes the "optimal" treatment environment of women with gynecologic cancer? *Gynecol Oncol*. 2003;89:1–3.
- Eisenkop SM, Spirtos NM. What are the current surgical objectives, strategies, and technical capabilities of gynecologic oncologists treating advanced epithelial ovarian cancer? *Gynecol Oncol*. 2001;82:489–497.
- Kitchener HC. Clinical practice guidelines: loss of clinical freedom or a coming of age? *Int J Gynecol Cancer*. 2002;12:332–236.
- Wolfe CD, Tilling K, Raju KS. Management and survival of ovarian cancer patients in south east England. *Eur J Cancer*. 1997;33:1835–1840.
- Hillner BE, Smith TJ, Desch CE. Hospital and physician volume or specialization and outcomes in cancer treatment: importance in quality of cancer care. *J Clin Oncol*. 2000;18:2327–2340.
- Mol BW, Boll D, De Kanter M, et al. Distinguishing the benign and malignant adnexal mass: an external validation of prognostic models. *Gynecol Oncol*. 2001;80:162–167.
- Im SS, Gordon AN, Buttin BM, et al. Validation of referral guidelines for women with pelvic masses. *Obstet Gynecol*. 2005;105:35–41.
- Munstedt K, Franke FE. Role of primary surgery in advanced ovarian cancer. *World J Surg Oncol*. 2004;2:32.
- Trimbos JB, Vergote I, Bolis G, et al. Impact of adjuvant chemotherapy and surgical staging in early-stage ovarian carcinoma: European Organisation for Research and Treatment of Cancer-Adjuvant Chemotherapy in Ovarian Neoplasm trial. *J Natl Cancer Inst*. 2003;95:113–125.
- van der Burg ME, van Lent M, Buyse M, et al. The effect of debulking surgery after induction chemotherapy on the prognosis in advanced epithelial ovarian cancer. Gynecological Cancer Cooperative Group of the European Organization for Research and Treatment of Cancer. *N Engl J Med*. 1995;332:629–634.
- Rose PG, Nerenstone S, Brady MF, et al. Secondary surgical cytoreduction for advanced ovarian carcinoma. *N Engl J Med*. 2004;351:2489–2497.